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Utility, reliability, sensitivity and factor structure of an online test system designed to
monitor changes in cognitive function in clinical trials

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Online cognitive testing in clinical trials

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The PROTECT study, Remote cognitive testing, attention, memory.

Key Points:

1. Individuals aged 50 to 94 years can undergo cognitive function testing via the internet
2. Baseline data for a 10-year trial were successfully gathered from 14,589 individuals
3. Testing was practical with 99.4% of tasks being completed
4. Clear age-related declines were identified on tests of attention, information processing and episodic memory

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DISCLOSURES

The CogTrack™ System is proprietary to Wesnes Cognition Ltd (www.wesnes.com). Keith Wesnes owns Wesnes Cognition Ltd and consults for various companies involved in clinical trials.

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ABSTRACT

Objective

The advent of long-term remotely conducted clinical trials requires assessments which can be administered online. This paper considers the utility, reliability, sensitivity and validity of an internet based system for measuring changes in cognitive function which is being used in one such trial.

Methods

The Platform for Research Online to investigate Genetics and Cognition in Ageing (PROTECT) is a 10 year longitudinal and entirely remote study launched in November 2015. The CogTrack™ System is being used to monitor changes in important aspects of cognitive function using tests of attention, information processing and episodic memory. On study entry the participants performed CogTrack™ up to three times over seven days, and these data are evaluated in this paper.

Results

During the first six months of the study, 14,589 individuals aged 50 to 94 years enrolled and performed the CogTrack™ System, 8,627 of whom completed three test sessions. On the first administration 99.4% of the study tasks were successfully completed. Repeated testing showed training/familiarisation effects on four of the seven measures which had largely stabilised by the third test session. The factor structure of the various measures was found to be robust. Evaluation of the influence of age identified clinically relevant declines over the age-range of the population being identified on one or more measures from all tasks.

Conclusions

The results of these analyses identify CogTrack™ to be a practical method to reliably, sensitively, remotely and repeatedly collect cognitive data from large samples of individuals aged fifty and over.

INTRODUCTION

Cognitive function is central to the quality of everyday behaviour. Many important aspects of cognitive ability have been established to decline with normal ageing (e.g. Salthouse, 2010a,b). As longevity continues to increase, for example a third of the population of the United Kingdom is now aged 50 years and over (www.ageuk.org.uk), the impact of these age-related cognitive declines becomes of greater importance. The direction of research into Alzheimer's disease (AD) and other major types of dementia has so far concentrated on the search for symptomatic treatments, however this approach is now facing a shift towards prophylaxis. Furthermore, although evidence accumulates for age-related cognitive decline throughout adulthood, both on functional and neurological levels, current thinking in this field is that 'Dementia is not an unavoidable consequence of ageing' (page 466, Winblad et al, 2016).

Assessments of cognitive function are widely used in many areas of research, and are essential to the field of cognition in ageing. Currently assessments are primarily achieved through the administration of various tasks to participants and patients by trained researchers. Automated cognitive testing can facilitate this process, though as with non-computerised testing, it is generally performed on a one-to-one basis in clinical settings. The cost and time implications of this requirement for clinical trials can impose methodological limitations both to study duration and to sample size (Fredrickson et al 2010). An important attribute of a cognitive task is its ability to be repeatedly administered over time, and under such circumstances to provide an accurate reflection of any changes which may occur (Goldberg et al, 2015; Wesnes and Pincock, 2012). Criteria for task methodology in clinical trials have long been established (e.g. Ferris et al, 1997), and require cognitive tasks which

have established practice profiles, can be reliably administered, have numerous equivalent forms, and can detect improvement as well as impairment with a high degree of sensitivity. With the increasing interest in age-related cognitive decline and the advent of trials in preclinical dementia, international work groups have stressed the need for inexpensive and reliable methods to achieve these aims and sensitively assess cognitive changes over time (e.g. Sperling et al 2011; Winblad et al, 2016).

A recent innovation is for clinical trials to be conducted without the need for participants to make visits to clinical facilities, instead the study data are gathered remotely (e.g. Orriá et al, 2014). In such trials which require the assessment of cognitive function, one solution would be for the participants to perform testing via the internet. Progress has already been made in this area, in one study over 90,000 individuals aged up to 104 years performed tests of cognitive function from the CDR System while browsing a herbal supplement website. The patterns of cognitive decline with ageing replicated the findings seen in published laboratory-based studies, confirming the potential of this approach (Wesnes, 2012; Wesnes & Edgar, 2014).

While such cross-sectional studies illustrate the potential of this approach, trials with repeated testing are essential, and represent a major opportunity for research into the ageing brain. Corbett et al (2015) conducted an online, double-blind, six month, three-arm randomized trial to assess the effects of a cognitive training (CT) package in healthy adults aged 50 years and above. Cognitive testing was performed at baseline, and again at 6, 12 and 24 weeks. Over a six week period 6,742 adults were recruited into the study. The study identified positive effects on the cognitive tasks in the groups randomized to CT compared

to controls. Importantly, the online assessment approach provided robust data, with good retention of participants.

Some of the most exciting trials in the field of ageing are longitudinal, such as the Cognitive Function and Ageing Studies (CFAS), a group of large population based studies assessing individuals aged 65 years and over, which began in 1989 (Matthews 2016). The obvious next step for such long-term population based studies is to avoid clinic visits, and one such study, PROTECT (Platform for Research Online to investigate Genetics and Cognition in Ageing), started in November 2015. PROTECT is a ten-year study in individuals aged 50 years and over, designed to determine the roles of lifestyle and genetic factors that contribute to the risk of cognitive decline, and also to develop and evaluate therapeutic interventions through nested clinical trials. Participants are required to provide information about health and wellbeing through the completion of various online questionnaires, and to undergo regular cognitive assessments of memory, attention and reasoning. Part of the assessment profile is CogTrack™, a newly developed set of online cognitive tasks to assess major aspects of cognitive function. The tasks are based on procedures which over the last 30 years have been widely used in worldwide clinical trials and have consistently shown high sensitivity and reliability (Wesnes et al, 2016). In PROTECT, the CogTrack™ tasks assess attention, information processing and pattern separation. This paper will present the CogTrack™ System data gathered over the first six months of the study, in order to evaluate the utility, reliability, sensitivity and factor structure of the system when used in adults aged 50 and over.

METHODS

Participants

Participants were adults over 50 living in the UK and recruited through the PROTECT study website. Participants were eligible for the study if they were 50 or older, had access to a computer and the internet and did not have a diagnosis of dementia. Recruitment of participants was achieved through local and national publicity and through invitation of individuals registered on existing research cohorts hosted by the Institute of Psychiatry, Psychology and Neuroscience at King's College London. Consent for involvement was given electronically through a secure online process. The PROTECT study gained ethical approval through the London Bridge NRES Committee (Reference: 13/LO/1578).

Procedure

Participants logged onto the PROTECT Website, and provided demographic, medical and lifestyle information based on items adapted from the Office of National Statistics. The participants were invited to complete an online set of cognitive tasks from the CogTrack™ System, with the option to perform the tasks on two further occasions within seven days, leaving a period of at least 24 hours between each assessment.

Education Level

The participants indicated the highest level of education completed from (1) Secondary Education (GCSE/O-Levels) to (5) Doctorate (PhD).

Assessment of Cognition

The CogTrack™ System is an online set of cognitive tasks (www.wesnes.com) based on procedures which have been used successfully over the last 30 years (Wesnes et al, 2016).

The instructions are presented visually at the start of each testing session, and also at the start of each task. In-task responses are made using the right arrow on the keyboard in two tasks, and the left and right arrows in the other two. The participants are instructed to rest their finger(s) lightly upon the key(s) throughout each task. The speed and accuracy of every response is recorded. The following tests were self-administered in the order below:

Pattern Separation Presentation: A series of 20 pictures of everyday scenes and objects is presented on the screen, at the rate of one picture every three seconds, for the participant to remember. The participant is instructed that the pictures will all be shown again later mixed with very similar ones.

Simple Reaction Time: The participant is instructed to press the right arrow key on the keyboard as quickly as possible every time a right-facing arrow containing the word 'YES' is presented in the centre of the screen. The participant is informed that only this stimulus will be presented and that it will remain there until a response is made. Fifty stimuli are presented with random inter-stimulus interval between one and 3.5 seconds.

Digit Vigilance: A target digit from one to nine is randomly selected and constantly displayed to the right hand side of the screen. A series of 450 digits is then presented one at a time in the centre of the screen at the rate of 150 per minute. The participant is required to press the right arrow key as quickly as possible every time a presented digit matches the target digit on the right.

Choice Reaction Time: The two possible stimuli in this task are either the right-facing arrow used in Simple Reaction Time, or a left facing version of the arrow, with the word 'NO' in the middle. On each of 50 successive trials, one of these two stimuli is selected randomly (but with equal probability) and presented in the centre of the screen, remaining there until a

response is made. The interval between successive trials varies randomly between one and 3.5 seconds. The participant is required to respond as quickly and accurately as possible.

Pattern Separation Recognition: The original pictures plus 20 very similar distractor (lure) pictures are presented one at a time, the order being counterbalanced such that half of the original pictures is presented prior to the distractor, and half afterwards. For each picture the participant has to indicate whether or not it was the precise picture shown earlier, pressing the right keyboard arrow if it was, and the left if it was not, as quickly and accurately as possible. Each picture remains on the screen until a response is made.

Statistical Analyses

The software package SAS® Version 9.4 was used to evaluate the data. In order to evaluate performance over the three test sessions, means and standard deviations were calculated, and Cohen's d effect sizes were calculated for the changes between the first and second, as well as the second and third performances of the tasks. Test-retest reliability was evaluated using Pearson's r correlations.

To evaluate the influence of age on performance, the subjects were divided into cohorts based on the age-distribution of the population. These data were submitted to ANCOVA using the procedure MIXED. Age-cohort, gender and the interaction between them were fitted to the model as fixed effects. The participants were fitted as a random effect. Education level was fitted as a covariate.

Evaluation of the factor structure of the tasks was conducted using the Principal Components Analysis (PCA) option in the FACTOR procedure. Factors which had eigenvalues greater than unity were selected for VARIMAX rotation.

RESULTS

Participants

A total of 14,531 participants performed the CogTrack™ tasks on one or more occasions between November 2015 and April, 2016. Of these, 10,270 (71%) were females aged 50 to 94 years (mean age 61.1 years, SD 6.9), while 4,261 (29%) were males aged 50 to 91 years (mean age 63.3 years, SD 7.6). The mean (SD) education levels of the females were 3.3 (1.4) and for the males 3.4 (1.4).

A total of 8,627 of these participants performed the tasks on three occasions during a seven day period, 6,270 (73%) being females aged 50 to 92 years (mean age 61.6, SD 6.9) and 2,357 (27%) males aged 50 to 91 (mean age 63.8, SD 7.5). The mean (SD) education levels of the females were 3.3 (1.4) and for the males 3.4 (1.5).

Utility and Practicality

For the 14,531 participants who performed the first test session, the data were successfully collected for 99.4% of the tasks. The missing task data were primarily due to a failure to complete the test session.

As the tasks were self-administered, it is also important to determine the clarity of the instructions as a measure of the utility and practicality of the CogTrack™ system. This was assessed for the first test performance by the 14,531 participants, searching for instances in which task performance suggested a lack of understanding of the instructions. For Simple Reaction Time, all participants completed the task with scores within the expected range for this age-group. In the Digit Vigilance Task, a failure to understand instructions would reflect very low rates of target detection or high numbers of false alarms. In the first performance

of the Digit Vigilance Task only two of the participants failed to detect a single target, and only six made more than 20 false alarms (range 21 to 34). Choice Reaction Time requires the participants to make 50 binary responses to stimuli which occur at unpredictable intervals but with equal probability. Participants who fail to understand this task would be expected to make correct responses at around chance levels, which occurred for four participants who scored 50% or below; the next lowest individual accuracy score being 68%, which is satisfactorily above chance. In the Pattern Separation Task participants are required to indicate whether or not each picture was shown previously. Failure to understand task requirements would result in recognition performance being at chance levels. In the Pattern Separation Task 97.7% of the participants scored above chance levels.

Stability over test sessions

The data presented in Table 1 indicate general stability of the various task measures, particularly after the initial testing session. Two notable changes from the first to second session occurred on the Pattern Separation Task. The ability to correctly identify the novel pictures increased by 13.3% in the second session (effect size 0.72), and while a further increase was seen from the second to the third session, this had reduced to a small effect size (0.2). The speed of correct identification of the original pictures slowed from the first to second session (effect size 0.46), but showed no meaningful change from the second to third session.

Impact of Age and Gender

The influences of age and gender were evaluated using data from the third test administration, as any familiarisation/training effects had largely stabilised by this session. Age-cohorts were created as follows: 50-54 years ($n=1,321$, 79% female), 55-59 years ($n=1,960$, 78% female), 60-64 years ($n=2,213$, 74.2% female), 65-69 years ($n=1,830$, 68.1% female), 70-74 years ($n=842$, 65.7% female), 75-79 years ($n=333$, 55.6% female), and 80-94 years ($n=128$, 56.3% female). The main effects of age-cohort and gender from the ANCOVAs, as well as the interactions between them are summarized in Table 2. Significant effects of age were seen on all ten measures, with the quality of performance declining over the successive age-cohorts. The overall Cohen's d effect sizes of the declines from the youngest to the oldest age-cohort exceeded large effects on five measures, and medium effects on a further two.

There were significant gender differences on seven of the measures, though only two exceeded the criterion of small effect sizes. One was for females to make an average of 0.61% more correct responses on choice reaction time (Cohen's $d = 0.24$). The other was for females to be more accurate in correctly rejecting the closely similar pictures in pattern separation (74.9% v 71.6%; Cohen's $d = 0.24$), although the speed of these responses was slightly but significantly faster for the males.

There were significant interactions between age-cohort and gender for six measures. Figures of the effects of age have thus been prepared showing the data for males and females separately. Figure 1 comprises of the measures from the Simple and Choice Reaction Time tasks. For Simple Reaction Time, speed declined steadily by age-cohort for females until the second oldest cohort. Males showed a similar pattern on this measure,

though the basis for the interaction between age and gender was most probably due to the differences between the genders in the 55-59 and 60-64 year cohorts. Choice Reaction Time showed a smoother pattern of decline for both genders, again the interaction being due to subtle differences in the pattern over time. The accuracy score from Choice Reaction Time failed to show any systematic changes with ageing, and had the smallest overall effect size (0.09).

Performance on the Digit Vigilance Task is presented in Figure 2. Speed of correct detections showed the clearest age-related declines, the interaction being best explained by the greater deficits shown by the males in the two oldest cohorts. The ability to correctly detect the targets did not show an effect of age until the declines seen with the oldest age group. The number of false alarms tended to increase with age, with males showing greater increases over the older age cohorts.

Performance on the Pattern Separation Task (Figure 3) indicates that the decline with ageing for the ability to correctly identify the closely similar pictures (Cohen's $d=1.16$) is greater than for the original pictures (Cohen's $d=0.29$). The significant interaction between age cohort and gender for the closely similar pictures appears to reflect greater declines for males in three of the age cohorts: 65-69, 70-74 and 74-79 years. The time taken to correctly identify the two types of stimuli declined markedly for both types of response, with effect sizes greater than 1. The decline can be seen to be greater for the closely similar pictures (Cohen's $d=1.54$) than for the original pictures (Cohen's $d=1.08$). Unlike the accuracy scores, the declines in the speed scores are slightly greater for the females.

Factor Analysis

The Principal Components Analysis (PCA) identified four factors with eigenvalues greater than unity, which accounted for 65.2% of the total variance, and were subject to VARIMAX rotation. The output of the rotation is presented in Table 3. The analysis identified factor loadings of 0.4 and above to be statistically reliable. The rotated factors were strong, having robust and significant loadings for all measures, and only one statistically reliable cross-loading. The measures from the three attention tasks loaded on two independent factors, one for the speed scores from the three tasks, and a second for the accuracy scores from Digit Vigilance and Choice Reaction Time. On the latter factor, false alarms loaded in the opposite direction to correct detections on the Vigilance task, supporting this factor to reflect the accuracy of sustained performance on the tasks. The other two factors concerned the Pattern Separation Task, with the accuracy scores loading on one factor, and the speed scores the other.

DISCUSSION

The baseline data gathered over the first six months of this longitudinal study have confirmed that individuals aged from 50 up to 94 years can satisfactorily and repeatedly undertake online cognitive testing using the CogTrack™ System.

Training and familiarity effects are known to occur with cognitive testing when repeated on the same individual (Goldberg et al, 2015; Wesnes & Pincock, 2002). In the present study three of the ten task measures showed training effects from the first to second sessions which exceeded a small effect size, these being the two accuracy scores on the Digit

Vigilance Task and the ability to reject the closely similar pictures in the Pattern Separation Task. These effects diminished notably by the third session. In contrast detection speed for original pictures in the Pattern Separation task slowed from the first to second session, and was stable thereafter. This pattern confirms the value of task familiarisation, and is further reflected in test-retest reliability scores which were superior for nine of the ten measures between the second and third test sessions, than between the first two.

As have been seen previously with such tasks (Salthouse 2010a,b; Wesnes et al, 2016), age-related deficits were seen on all measures, these being of clinically relevant magnitude for one or more measures from all tasks, and for three tasks deficits on one or more measures of three tasks, these exceeded the threshold for large effects. The patterns of decline varied slightly between males and females.

An important stage in the validation of a test system is the evaluation of the factor structure of the various task measures. The analysis identified four independent factors, the overall pattern being directly comparable to the factor structure reported previously by Wesnes et al (2000) using the same analysis technique for the CDR System tasks upon which the CogTrack™ tasks are based. This replication of the factor structure seen previously for the CDR System tasks supports the ability of the CogTrack™ System tasks in the present study to independently assess four important domains of cognitive function.

The requirement for appropriate measures of cognitive function in this field has recently been emphasised by The Lancet Neurology Commission which emphasises the need for new cognitive assessment batteries with reduced variation in outputs from repeat testing, as well as improved instructions and simple delivery models to reduce confounding effects, for example from variation in language skills. (Page 487; Winblad et al, 2016). There is an

emerging consensus that standardised online cognitive testing represents a promising solution to this research need. Overall, the analysis reported here provides robust data from a large cohort that supports the utility and validity of the CogTrack™ System in measuring cognitive function through an online platform. The potential applications of this approach are extremely broad, particularly considering the current expansion of remote testing and online technology within healthcare, which could have direct implications for diagnostics, clinical trial design and precision medicine approaches for public health.

CONCLUSION

PROTECT has established that the internet is a suitable platform to engage large numbers of participants in long-term research projects. The data presented in this paper strongly suggest that CogTrack™ is a reliable, valid and sensitive online system for the repeated assessment of cognitive function in such studies.

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Table 1. Performance over the three repeated sessions with test-retest reliability

CogTrack™ measure	Session 1	Session 2	Session 3	Cohen's d		Test-Retest Pearson's r	
	Mean (SD)	Mean (SD)	Mean (SD)	Session 1 to 2	Session 2 to 3	Session 1 to 2	Session 2 to 3
Simple Reaction Time (ms)	344 (74)	340 (54)	340 (50)	0.06	0.00	0.54	0.75
Choice Reaction Time (ms)	519 (70)	515 (65)	513 (64)	0.06	0.03	0.73	0.81
Choice Reaction Time Accuracy (%)	97.5 (2.6)	97.5 (2.7)	97.5 (2.6)	0.00	0.00	0.50	0.50
Digit Vigilance Correct Detections (%)	97.3 (6)	98.3 (4.1)	98.6 (3.8)	0.20	0.08	0.19	0.25
Digit Vigilance False Alarms (#)	2.31 (2.3)	1.6 (1.8)	1.34 (1.6)	0.35	0.15	0.46	0.43
Digit Vigilance Detection Speed (ms)	486 (46)	487 (45)	488 (46)	0.02	0.02	0.78	0.81
Pattern Separation Original Stimuli Accuracy (%)	91.1 (8.8)	91.2 (8.5)	91.4 (8.1)	0.01	0.02	0.19	0.29
Pattern Separation Lure Stimuli Accuracy (%)	60.4 (21)	73.7 (16)	76.8 (15)	0.72	0.20	0.53	0.60
Pattern Separation Original Stimuli speed (ms)	1158 (277)	1296 (320)	1288 (298)	0.46	0.03	0.52	0.66
Pattern Separation Lure Stimuli speed (ms)	1517 (481)	1499 (388)	1447 (365)	0.04	0.14	0.51	0.60

Table 2. Summary outcomes of ANCOVAs conducted on the age-cohorts and gender.

Measure	Age-Cohort				Gender						Age-Cohort *Gender	
	F df 6,8363	p	Decline LSMeans (sem) *	d	F df 1,8363	P	Females LSMeans (sem)	Males LSMeans (sem)	Difference LSMeans (sem)	d	F df 6,8363	P
Simple Reaction Time (ms)	23.12	<.0001	25.8 (4.8)	0.52	0.43	0.5117	344.1 (1.1)	345.2 (1.4)	1.2 (1.8)	0.02	2.75	0.0115
Choice Reaction Time (ms)	76.56	<.0001	62.2 (6)	1.01	0.6	0.4374	521.8 (1.4)	523.6 (1.7)	1.7 (2.2)	0.03	3.02	0.006
Choice Reaction Time Accuracy (%)	3.9	0.0007	-0.23 (0.25)	0.09	44.32	<.0001	97.6 (0.06)	97.0 (0.07)	0.61 (0.09)	0.24	1.91	0.075
Digit Vigilance Correct Detections (%)	4.8	<.0001	-1.47 (0.37)	0.39	11.02	0.0009	98.5 (0.09)	98.0 (0.11)	0.46 (0.14)	0.12	0.85	0.5285
Digit Vigilance False Alarms (#)	26.97	<.0001	0.99 (0.15)	0.63	13.99	0.0002	1.46 (0.04)	1.67 (0.04)	0.21 (0.06)	0.14	2.75	0.0114
Digit Vigilance Detection Speed (ms)	58.46	<.0001	45.4 (4.4)	1.01	5.08	0.0242	494.7 (1.0)	498.4 (1.3)	3.7 (1.6)	0.08	4.1	0.0004
Pattern Separation Original Stimuli Accuracy (%)	5.15	<.0001	-2.33 (0.78)	0.29	1.99	0.158	91.0 (0.18)	90.6 (0.23)	0.41 (0.29)	0.05	0.42	0.8655
Pattern Separation Lure Stimuli Accuracy (%)	87.12	<.0001	-16.49 (1.38)	1.16	40.62	<.0001	74.9 (0.32)	71.6 (0.40)	3.27 (0.51)	0.23	2.85	0.0089
Pattern Separation Original Stimuli speed (ms)	75.95	<.0001	313.7 (28.2)	1.08	20.83	<.0001	1350 (6.5)	1311 (8.2)	47.8 (10.5)	0.17	2.46	0.0222
Pattern Separation Lure Stimuli speed (ms)	113.49	<.0001	534.8 (33.9)	1.54	5.52	0.0188	1548 (7.8)	1519 (9.8)	29.6 (12.6)	0.09	2.02	0.0595

*Note the decline is from the youngest to oldest age-cohort

Table 3: Output of principal components analysis showing the Varimax rotated factor structure of the various measures from the CogTrack™ tasks used in this study. The significant factor loadings on the four factors are shown in bold

TASK MEASURES	Factor 1	Factor 2	Factor 3	Factor 4
	Eigenvalues			
	2.26	1.58	1.34	1.34
Simple Reaction Time (ms)	0.83	0.07	0.17	-0.05
Choice Reaction Time (ms)	0.80	0.26	0.02	-0.07
Digit Vigilance Detection Speed (ms)	0.80	0.12	-0.11	0.00
Pattern Separation Original Stimuli speed (ms)	0.13	0.87	0.00	-0.01
Pattern Separation Lure Stimuli speed (ms)	0.20	0.82	-0.03	-0.18
Choice Reaction Time Accuracy (%)	0.26	0.05	0.63	0.04
Digit Vigilance Correct Detections (%)	-0.41	0.13	0.57	0.07
Digit Vigilance False Alarms (#)	0.02	0.14	-0.76	-0.02
Pattern Separation Lure Stimuli Accuracy (%)	-0.04	-0.09	0.06	0.81
Pattern Separation Original Stimuli Accuracy (%)	-0.03	-0.06	0.03	0.79